Amendments to the Claims:

This listing of claims will replace all prior versions and listings, of claims in the application:

Listing of Claims:

1. ***(Currently Amended)*** A computer-aided method of docking a ligand to a protein having a binding site, said method comprising:

performing a pre-docking conformational search ~~to~~ and generating ~~generate~~ multiple solution conformations of the ligand ~~in solution~~therefrom;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one conformation of the multiple solution conformations of the ligand ~~in solution~~ to obtain at least one position of the ligand relative to the protein in a protein-ligand complex; and

optimizing the at least one position of the ligand while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed.

2. ***(Currently Amended)*** The method of claim 1, ~~wherein~~ additionally comprising, after ~~said~~ performing the pre-docking conformational search and generating multiple solution conformations, creating a database of the multiple solution conformations of the ligand ~~in solution~~ and storing said three-dimensional database for subsequent use by said matching.

3. ***(Currently Amended)*** The method of claim 2, wherein said database of the multiple solution conformations of the ligand ~~in solution~~ comprises a conformational database of a combinatorial library.

4. ***(Currently Amended)*** The method of claim 1, wherein said performing the pre-docking conformational search and generating multiple solution conformations of the ligand comprises:

randomly generating a plurality of conformations of the ~~molecule~~ligand;

minimizing a strain of each conformation of the plurality of conformations;

using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple conformations of the ligand in solution.

5. ***(Original)*** The method of claim 1, wherein said generating the binding site image includes at least one of creating a list of a polar hot spots identifying points in the binding site that are favorable for an a polar atom to bind, and generating a list of polar hot spots identifying points in the binding site that are favorable for a hydrogen bond donor or acceptor to bind.

6. ***(Previously Presented)*** The method of claim 5, wherein said generating the binding site image further comprises:

placing a grid around the binding site of the protein;

determining a hot spot search volume using said grid;

determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, clustering the hot spots and retaining a desired number of top clusters of hot spots, said desired number of top clusters comprising said multiple hot spots to be employed by said matching.

7. ***(Currently Amended)*** The method of claim 1, wherein said matching comprises:

matching atoms of the at least one solution conformation of the ligand ~~in solution~~ to appropriate hot spots of the protein by positioning the at least one solution conformation of the ligand ~~in solution~~ as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the ~~molecule~~ ligand ~~in solution~~ into the binding site of the protein.

8. ***(Currently Amended)*** The method of claim 7, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

I(R,T) = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation of the ligand ~~in solution~~;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation of the ligand ~~in solution~~;

R = a 3x3 rotation matrix; and

T = a translation vector.

9. ***(Previously Presented)*** The method of claim 1, wherein multiple positions of the ligand are obtained, and said optimizing step comprises :

eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the ligand and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

10. ***(Previously Presented)*** The method of claim 9, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.

11. ***(Currently Amended)*** A computer-aided system for docking a ligand to a protein having a binding site, said system comprising:

means for performing a pre-docking conformational search ~~to generate~~ and generating multiple solution conformations of the ligand ~~in solution~~ therefrom;

means for generating a binding site image of the protein, said binding site image comprising multiple hot spots;

means for matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple conformations of the ligand ~~in solution~~ to obtain at least one position of the ligand relative to the protein in a protein-ligand complex; and means for optimizing the at least one position of the ligand while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed.

12. ***(Currently Amended)*** The system of claim 11, ~~wherein said~~ additionally comprising ~~means for performing the pre-docking conformational search comprises~~ means for creating a database of the multiple solution conformations of the ligand ~~in solution~~ and for storing said three-dimensional database for subsequent use by said matching, after performing the pre-docking conformational search and generating multiple solution conformations of the ligand.

13. ***(Currently Amended)*** The system of claim 12, wherein said database of the multiple solution conformations of the ligand ~~in solution~~ comprises a conformational database of a combinatorial library.

14. ***(Currently Amended)*** The system of claim 11, wherein said means for performing the pre-docking conformational search and generating multiple solution conformations of the ligand comprises:

means for randomly generating a plurality of conformations of the ligand;

means for minimizing a strain of each conformation of the plurality of conformations;

means for using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

means for clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple solution conformations of the ligand ~~in solution~~.

15. ***(Original)*** The system of claim 11, wherein said means for generating the binding site image includes at least one of means for creating a list of apolar hot spots identifying points in the binding site that are favorable for an apolar atom to bind, and means for generating a list of polar hot spots identifying points in the binding site that are favorable for a hydrogen bond donor or acceptor to bind.

16. ***(Previously Presented)*** The system of claim 15, wherein said means for generating the binding site image further comprises:

means for placing a grid around the binding site of the protein;

means for determining a hot spot search volume using said grid;

means for determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, means for clustering the hot spots and for retaining a desired number of top clusters of hot spots, said desired number of top clusters comprising said multiple hot spots to be employed by said matching.

17. ***(Currently Amended)*** The system of claim 11, wherein said means for matching comprises:

means for matching atoms of the at least one solution conformation of the ligand ~~in solution~~ to appropriate hot spots of the protein by positioning the at least one solution conformation of the ligand ~~in solution~~ as a rigid body into the binding site image;

means for defining a match, said match determining a unique rigid body transformation; and

means for using the unique rigid body transformation to place the at least one solution conformation of the ligand ~~in solution~~ into the binding site of the protein.

18. ***(Currently Amended)*** The system of claim 17, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

I(R,T) = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation of the ligand ~~in solution~~;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation of the ligand ~~in solution~~;

R = a 3x3 rotation matrix; and

T = a translation vector.

19. ***(Previously Presented)*** The system of claim 11, wherein multiple positions of the ligand are obtained, and said means for optimizing comprises :

means for eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

means for ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, means for clustering the positions of the ligand and selecting a top number n of positions; and

means for optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

20. ***(Previously Presented)*** The system of claim 19, wherein said means for optimizing comprises means for optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.

21. ***(Currently Amended)*** At least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of docking a ligand to a protein having a binding site, said method comprising:

performing a pre-docking conformational search ~~to generate~~ and generating multiple solution conformations of the ligand ~~in solution~~ therefrom;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one conformation of the multiple solution conformations of the ligand ~~in solution~~ to obtain at least one position of the ligand relative to the protein in a protein-ligand complex; and

optimizing the at least one position while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed.

22. ***(Currently Amended)*** The at least one program storage device of claim 21, ~~wherein said~~ additionally comprising, after performing the pre-docking conformational search and generating multiple solution conformations of the ligand, creating a database of the multiple

solution conformations of the ligand ~~in solution~~ and storing said three-dimensional database for subsequent use by said matching.

23. ***(Currently Amended)*** The at least one program storage device of claim 22, wherein said database of the multiple solution conformations of the ligand ~~in solution~~ comprises a conformational database of a combinatorial library.

24. ***(Currently Amended)*** The at least one program storage device of claim 21, wherein said performing the pre-docking conformational search and generating multiple solution conformations of the ligand comprises:

randomly generating a plurality of conformations of the ligand;

minimizing a strain and a solvent accessible surface area of each conformation of the plurality of conformations;

using the strain of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple solution conformations of the ligand ~~in solution~~.

25. ***(Original)*** The at least one program storage device of claim 21, wherein said generating the binding site image includes at least one of creating a list of apolar hot spots identifying points in the binding site that are favorable for an apolar atom to bind, and generating a list of polar hot spots identifying points in the binding site that are favorable for a hydrogen bond donor or acceptor to bind.

26. ***(Previously Presented)*** The at least one program storage device of claim 25, wherein said generating the binding site image further comprises:

placing a grid around the binding site of the protein;

determining a hot spot search volume using said grid;

determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, clustering the hot spots and retaining a desired number of top clusters of hot spots, said desired number of top clusters comprising said multiple hot spots to be employed by said matching.

27. ***(Currently Amended)*** The at least one program storage device of claim 21, wherein said matching comprises:

matching atoms of the at least one solution conformation of the ligand ~~in solution~~ to appropriate hot spots of the protein by positioning the at least one solution conformation of the ligand ~~in solution~~ as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the ligand ~~in solution~~ into the binding site of the protein.

28. ***(Currently Amended)*** The at least one program storage device of claim 27, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

I(R,T) = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation of the ligand ~~in solution~~;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation of the ligand ~~in solution~~;

R = a 3x3 rotation matrix; and

T = a translation vector.

29. ***(Previously Presented)*** The at least one program storage device of claim 21, wherein multiple positions of the ligand are obtained, and said optimizing step comprises :

eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the ligand and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

30. ***(Previously Presented)*** The at least one program storage device of claim 29, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.